

REMARKS

Status of Claims

Where appropriate, the language of the claims has been amended in order to comply with the indefiniteness requirements set forth by the Examiner, as well as to provide additional clarity by abbreviating the term "T-cell costimulatory cell adhesion molecule" as "CAM" where appropriate, i.e., in all occurrences after the first occurrence, where, in keeping with the requirements of the United States Patent and Trademark Office the term is written out in full. No new matter has been added by way of these amendments.

After amendment, claims 1-4, 12-14, 20-22, 28-30, 36-38, and 44-46 are pending.

The Rejection of The Claims Under 35 U.S.C. § 112, First Paragraph As Lacking Adequate Enablement Must Be Withdrawn

The Examiner has rejected claims 44-46 as depending upon non-existing claims. In this regard, Applicants note that the reference in claim 44 to claim 62 should have been to claim 6, and that the reference in claim 46 to claim 61 should similarly have been to claim 6. These errors occurred as a result of two uncorrected OCR errors, which Applicants have now corrected in the claims as currently presented. Applicants thank the Examiner for identifying these errors and bringing them to the attention of Applicants.

The Examiner has rejected claims 3, 4, 28-30, 36-38, and 44-46 as indefinite for the recitation of a variety of unclear clauses in these claims, as specifically identified by the Examiner in the Office Action. With regard to this rejection as it applies to claim 3, and the claims that depend therefrom, Applicants have now

amended the claims to provide additional clarity, and this rejection should therefore be withdrawn.

With regard to this rejection as it applies to claim 4, and the claims that depend therefrom, Applicants respectfully note that, as is clearly provided in this claim, the method step is that of pre-administration of the CAM, and the composition for this step clearly comprises said CAM. Therefore, Applicants respectfully request that the Examiner withdraw the rejection as it applies to this portion of the claims.

The Rejection of The Claims Under 35 U.S.C. § 103(a) As Obvious Must Be Withdrawn

The Examiner has maintained her rejection of all of the currently pending claims as obvious. Specifically, in the previous Office Action of 1/16/07, the Examiner had asserted that the claims were obvious in light of the combination of Futami et al. (J. Immunotherapy 12:247 (1992), hereinafter "Futami") and Olsson et al. (Intl. Immunol. 10:499 (1998), hereinafter "Olsson"). In their Response of 7/16/07, Applicants noted that, apart from other reasons why the rejection was inapposite, neither Futami nor Olsson taught the DMXAA of the claims, and therefore no *prima facie* case for obviousness had been established by the Examiner. In response, in the present Office Action the Examiner has now provided a third reference, Wilson et al. (Int. J. Rad. Onc. Biol. Phys. 47:905 (1998), hereinafter "Wilson"), which the Examiner asserts provide the DMXAA of the invention, i.e., that the three references of Futami + Olsson + Wilson provide a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

With regard to the above argument, as Applicants will show in detail below, just as for Futami + Olsson, the three-fold combination of Futami + Olsson + Wilson still does not provide any basis for an obviousness rejection. Moreover, as

Applicants will also show, the entire thrust of the Examiner's argument constitutes impermissible hindsight, and not evidence of any rational motivation to combine or sufficiency of such combination as providing a *prima facie* case of obviousness.

1. The Examiner's Logic For The 1/16/07 35 U.S.C. § 103(a) Rejection

In the obviousness rejection of 1/16/07 the Examiner based her rejection on four assertions:

1. That Futami teaches DMXAA and IL-2 in combination to treat cancer;
2. That Olsson teaches that the presence of IL-2 may be substituted for by the CAM B7.1;
3. That it would have been obvious to combine these references; and,
4. That, when combined such that the IL-2 of Futami is replaced by the CAM B7.1 of Olsson, both the DMXAA and CAM B7.1 of the invention are taught, thereby rendering the invention obvious.

2. Applicants Response of 7/16/07 Showed The Numerous Deficiencies In The Examiner's Logic, Including The Failure Of Either Futami Or Olsson To Teach DMXAA

In their Response of 7/16/07, Applicants showed the numerous deficiencies in the Examiner's argument regarding obviousness, and perhaps most fundamentally the fact that neither Futami nor Olsson teach the DMXAA of the invention. Specifically, although Applicants explicitly reassert all of their previous arguments, for the present Response it will be appropriate to focus on the fact that neither Futami nor Olsson taught DMXAA, and in fact the data of Futami explicitly showed that different chemicals related to DMXAA behaved differently, with only some working, thereby effectively teaching away from any compounds other than those used, i.e., effectively teaching away from the use of DMXAA.

3. In Response, In The Current Office Action The Examiner Has Attempted To Provide The DMXAA Aspect Of The Invention By The Inclusion Of A THIRD Reference, Wilson

In the current Office Action of 10/9/07, the Examiner has now provided a third reference, Wilson, which the Examiner argues provides the DMXAA of the invention. Thus, the Examiner asserts, the combination of Futami + Olsson + Wilson provides every aspect of the DMXAA + CAM B7.1 of the present invention as embodied in the claims, and therefore renders these claims obvious.

4. The Production Of Wilson Represents A Failure To Follow The Searching Procedures Of MPEP § 904.03 And Represents An Unnecessary Expenditure Of Applicants' Patent Term and Money

At the outset, Applicants respectfully note that it is clear from a brief review of Futami and Olsson that neither reference teach DMXAA. Therefore, Applicants respectfully submit that the Examiner should have produced any references providing DMXAA – and specifically Wilson – earlier in prosecution, rather than now, where both patent term and attorney fees have been unnecessarily spent by Applicants as a result of the Examiner's failure to earlier provide this reference.

In this regard, Applicants note that the Manual of Patent Examining Procedure ("MPEP") § 904.03 specifically states that:

It is a prerequisite to a speedy and just determination of the issues involved in the examination of an application that a careful and comprehensive search, commensurate with the limitations appearing in the most detailed claims in the case, be made in preparing the first action on the merits so that the second action on the merits can be made final or the application allowed with no further searching other than to update the original search. It is normally not enough that references be selected to meet only the terms of the claims alone, especially if only broad claims are presented; but the search should, insofar as possible, also cover all subject matter which the examiner

reasonably anticipates might be incorporated into applicant's amendment.

Thus on this basis, Applicants respectfully presume either that there will be no further searches, or that such searches will now be more complete, thereby obviating the need for more patent term loss or expense on the part of Applicants.

5. Wilson Teaches DMXAA, But Does NOT Teach IL-2, And Therefore CANNOT Be Used To Fit The Examiner's Logic Nor To Replace That Which Is Already Absent In Futami

Referring back to the Examiner's logic behind the obviousness rejection, which Applicants have shown in summary form in #1 above, it is clear that, in order for this logic to work, there MUST be one reference that teaches DMXAA and IL-2, and another reference that teaches CAM B7.1 giving rise to IL-2.

Previously, Applicants demonstrated that the first condition above was not satisfied by either Futami or Olsson, since neither of those references teach DMXAA and IL-2.

With regard to Wilson, Applicants state uncategorically that this reference similarly does not provide both DMXAA and IL-2, and therefore no more satisfies the Examiner's logic than did Futami or Olsson. Thus the Examiner states in the Office Action that DMXAA is used in combination with radiation therapy, which is certainly not the combination of agents used in the present invention. And, although the Examiner also states that "Wilson et al. also teach that DMXAA induces synthesis of TNF" (Office Action page 4), TNF is irrelevant to the Examiner's claim of the combination of Futami + Olsson + Wilson, since the link to CAM B7.1 is, according to the Examiner, the result of this CAM's involvement in IL-2 expression, as taught in Olsson.

6. The Examiner's Own Statements Regarding Unpredictability Defeat Any Claim On The Examiner's Part Of A *Prima Facie* Case Of Obviousness

The fact that the logic of the Examiner's assertion is not satisfied by the triple combination of Futami + Olsson + Wilson is, by itself, reason enough to withdraw the obviousness rejection. However, an additional reason for the withdrawal of this rejection is that, by the Examiner's own statements, the art underlying the combinations of compounds of the invention is so unpredictable that such combinations would have no reasonable expectation of success, as is required for a showing of *prima facie* obviousness.

Specifically, in the Office Action of 8/23/06, on page 4, the Examiner explicitly asserted that finding synergistic combinations of drugs requires extensive testing, i.e., is an art with no reasonable expectation of success:

One skilled in the art recognizes that the search for combinations of drugs (each has less effect when it is used alone) exerting a combined effect requires a great deal of empirical testing of agents known to have anti-cancer properties or that may augment an agent having anti-cancer properties (Gerson et al, WO03/070234, page 2, lines 11-14). In addition, not all the analogue of XAA has a tumor restricted function, Futami et al., (J of Immunotherapy, vol 12, 247-255) indicates that 7-methyl-XAA, a analogue of XAA, self, or combination with IL-2 has not synergistic activity in suppression of tumor growth (page 252-253, col 1). Thus, it would be undue experimentation to test two agents in combination in order to determine whether one skilled in the art could use them together for treating a large or advanced tumor.

(emphases added). In this regard the Examiner further cited to Gerson to support her claim, and specifically to page 2, lines 7-14 of Gerson, which state:

The design of drug combinations for the chemotherapeutic treatment of cancer should be approached with the goals of 1) finding a combination that is synergistic with and not merely additive to the first compound with respect to the 10 elimination of the tumor, and 2) finding a second drug that does not potentiate the toxic effects of the

first chemotherapeutic agent. These conditions require a great deal of empirical testing of agents known to have anticancer properties with agents that either may have anticancer properties, or that may augment the first agent in other ways.

(emphasis added).

In this regard, if the Examiner believes that there is no reasonable expectation of success in combining different drugs, how can the Examiner possibly claim that such expectation of success exists for combining the disparate and non-relating results for different compounds of the TRIPLE combination of Futami + Olsson + Wilson?

The only such basis for this claim is that, apparently, the Examiner believes both that such combinations are unpredictable and are also routine. Specifically, on page 6, last paragraph, of the current Office Action the Examiner states "combining the anti-cancer agents to form a new protocol is routine for one skilled in the art to practice the cancer treatment" (emphasis added). It is obviously impossible for something to be at the same time predictable and un-predictable, and the obviousness rejection should be withdrawn on this additional basis.

7. The Examiner Appears To Misunderstand The Results Of Futami

With regard to the analyses of the previous sections, Applicants reiterate that there is no basis whatsoever for the obviousness rejection the Examiner has asserted. In this regard, Applicants note that, although the Examiner's analyses are, by and large, exemplary in their detail, it is possible that the Examiner is confused as to the results of Futami, since the Examiner continues to assert that Futami teaches DMXAA, when in fact it does not.

Thus at the outset, Applicants thank the Examiner for her generally careful reading of the art at issue. However, twice in the current Office Action the Examiner

misreads the teaching of Futami as including DMXAA, when in fact this reference does not teach DMXAA.

Thus on page 4, last paragraph, the Examiner states that “both Wilson et al., and Futami have already shown the advantage of the tumor therapy by potentiating or synergistic response for the large tumor in combination of anti-tumor treatment with DMXAA” (emphasis added), when in fact this statement is emphatically not true for Futami. Similarly on page 6, first full paragraph the Examiner states that “the references by Futami et al. and Wilson et al., teach treating tumor with DMXAA in combination with IL-2, not with B7.1” (emphasis added), a statement that again is not true with regard to Futami.

With regard to the above, and as previously stated, neither Futami nor Wilson satisfy the logic of the Examiner’s argument, and therefore do not support the Examiner’s assertion that the claims are obvious.

8. The Examiner’s Argument Constitutes Impermissible Hindsight

In the present Office Action the Examiner has added a reference (Wilson) to the two previously cited (Futami and Olsson), and argued that all three of these references in combination render the currently pending claims obvious. In light of the above discussions, it is clear that the Examiner has obtained these three references for combination based on an impermissible hindsight analysis, specifically an analysis in which an endpoint – DMXAA and the CAM B7.1 – leads to the identification of the references, and not vice-versa.

In this regard, Applicants reiterate that the use of IL-2 does not imply the use of CAM B7.1, as there are many inducing agents for IL-2. Respectfully, the Examiner has selected this “connection” only because it allows for a claim of obviousness. And, as Applicants have shown, this claim cannot be sustained because none of the references cited teach DMXAA and IL-2.

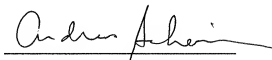
Conclusion

In light of the foregoing, Applicants submit that claims all of the pending claims, i.e., claims 1-4, 12-14, 20-22, 28-30, 36-38 and 44-46, are in condition for allowance and such allowance is respectfully requested. Should the Examiner feel that any unresolved issues remain in this case, the Examiner is encouraged to contact the undersigned at the telephone number listed below to discuss these issues.

The Commissioner is hereby authorized to charge a fee of \$120 for the one-month extension of time and any other fee that may have been overlooked to Deposit Account No. 10-0223.

Respectfully submitted,

Dated: 2/11/08



Andrew O. Scheinman
Reg. No. 50,730

JAECKLE FLEISCHMANN & MUGEL, LLP

190 Linden Oaks

Rochester, New York 14625-2812

Tel: (585) 899-2930

Fax: (585) 899-2931